1: J Clin Immunol 1990 Nov;10(6 Suppl):30S-38S; discussion 38S-39S

The use of monoclonal antibodies for treatment of autoimmune disease.

Steinman L.

Department of Neurology and Genetics, Stanford University, California 94305.

Over the past decade monoclonal antibodies have been successfully employed in a number of animal models of autoimmune disease. We have used antibodies to the class II gene products of the major histocompatibility complex, the CD4 molecule on helper T cells, and the T-cell receptor. Monoclonal anti-class II antibodies have been administered to treat paralytic disease in the animal model of multiple sclerosis--experimental allergic encephalomyelitis. These antibodies not only reverse acute paralytic disease but also decrease the number of relapses in a model of relapsing/remitting multiple sclerosis when given after the first attack. The advantage of this form of therapy is that it is haplotype specific. In other words, in a heterozygous individual it is possible to block the major histocompatibility gene associated with disease susceptibility while leaving other major histocompatibility gene products free for antigen presentation. Thus, animals given this form of immunotherapy are not significantly immunosuppressed. Antibodies to the CD4 molecule have been equally effective in treating animal models of autoimmunity. We and others have reversed ongoing paralysis in experimental autoimmune encephalomyelitis. Relapses have been diminished after the administration of anti-CD4. Antibodies to CD4 have been used successfully to treat animal models of systemic lupus erythematosus, rheumatoid arthritis and myasthenia gravis. Recent trials with anti-CD4 have been successful in the treatment of rheumatoid arthritis and cutaneous T-cell lymphoma. The latter trial employed a chimeric human/mouse antibody. Antibodies to the variable region of the T-cell receptor have been employed to treat experimental autoimmune encephalomyelitis.(ABSTRACT TRUNCATED AT 250 WORDS)

Publication Types:
- Review

☐ 1: J Clin Immunol 1990 Nov;10(6 Suppl):30S-38S; discussion 38S-39S

The use of monoclonal antibodies for treatment of autoimmune disease.

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Publication Types:
- Review

☐ 1: DNA Cell Biol 1990 Jun;9(5):347-53

Expression and characterization of human CD4:immunoglobulin fusion proteins.

Zettlmeissl G, Gregersen JP, Duport JM, Mehdi S, Reiner G, Seed B.

Research Laboratories of Behringwerke AG, Marburg, West Germany.

Different chimeric antibody-like molecules consisting of the four human CD4 extracellular domains (amino acids 1-369) fused to different parts of human IgG1 and IgM heavy-chain constant regions have been created and expressed in mammalian cells. For both IgG1 and IgM fusion proteins, the best expression in COS cells was observed for molecules lacking the CH1 domain of the heavy-chain constant region. The chimeric molecules are potent inhibitors of human immunodeficiency virus (HIV) infection and HIV-mediated cytotoxicity. A CD4:IgG1 hinge fusion protein, which was analyzed in more detail, binds efficiently to HIV gp160 and human Fc receptors and shows complement-assisted inhibition of viral propagation in culture. Half-life studies after intravenous application of the latter human fusion protein into mice and monkeys showed significant prolongation of serum survival compared to soluble CD4. An IgG2b murine homolog of the human CD4:IgG1 hinge fusion protein was prepared and evaluated in mice, where it was found to be nontoxic and to have no detectable effect on the humoral response to soluble antigen.

PMID: 2196903 [PubMed - indexed for MEDLINE]

1: Arthritis Rheum 1991 May;34(5):525-36 Related Articles, Books, LinkOut

Treatment of rheumatoid arthritis with monoclonal CD4 antibody M-T151. Clinical results and immunopharmacologic effects in an open study, including repeated administration.

Reiter C, Kakavand B, Rieber EP, Schattenkirchner M, Riethmuller G, Kruger K.

Institute for Immunology, University of Munich, Germany.

Recent experimental and clinical data point to the T helper lymphocyte subset as playing a central role in the pathogenesis of rheumatoid arthritis (RA). Thus, a therapeutic strategy aimed specifically at the CD4 T cell subset is warranted. We treated patients with active RA for 7 days with a daily dose of 20 mg of CD4 monoclonal antibody M-T151, administered intravenously over 30 minutes. There were no negative side effects. According to changes in the combined parameters of Ritchie articular index, pain assessment, grip strength, and morning stiffness, 6 patients had a good response. Clinical improvement was greatest approximately 2 weeks after termination of the therapy and lasted from 4 weeks to 6 months. Of the serologic parameters of inflammation, only the C-reactive protein level improved in the patients with a favorable response. Close immunologic monitoring revealed a transient, selective depletion of CD4+ T cells after each infusion. During the entire treatment period, residual circulating CD4+ cells were found to be coated with CD4 antibody, whereas free antibody was detected in the serum only for approximately 8 hours after each infusion. Immediately after infusion, soluble CD4 antigen appeared in the serum. In addition to the cell-bound CD4 antibody, complement components could be detected on the surface of the remaining CD4+ cells. The proliferative response of peripheral blood mononuclear cells to purified protein derivative was significantly diminished 4 weeks after cessation of antibody treatment. Six patients showed a weak antibody response to mouse immunoglobulin. In 4 of the responders who received a second course of therapy (2 of them as outpatients), a therapeutic effect was noted that was similar to that after the first course. Only 1 patient, who had low titers of serum IgE anti-mouse Ig antibodies, showed a mild anaphylactic reaction at the end of the second course of therapy. Treatment of RA with the monoclonal CD4 antibody M-T151 seems to be a promising alternative, although the optimal dose and the regimen of administration are still to be defined.

☐ 1: Arthritis Rheum 1991 Feb;34(2):129-40 Related Articles, Books, LinkOut

Treatment of rheumatoid arthritis with an anti-CD4 monoclonal antibody.

Horneff G, Burmester GR, Emmrich F, Kalden JR.

Max Planck Clinical Research Unit for Rheumatology/Immunology, Department of Medicine III, University of Erlangen-Nurnberg, FRG.

The effect of treatment with a monoclonal antibody against the CD4 antigen present on T helper cells was studied in 10 patients with severe intractable rheumatoid arthritis. In an open trial, monoclonal antibody 16H5 was infused at a dosage of 0.3 mg/kg of body weight on 7 consecutive days. Studies of the kinetics demonstrated a drastic depletion of CD4+ cells, to as low as 25 cells/microliters, 1 hour after the first infusion. The subsequent recovery of the CD4+ cell numbers 24 hours after infusion did not reach initial levels, and after the full 7-day treatment cycle there was a significant reduction of the number of CD4+ cells (mean +/- SD 51 +/- 28%; P less than 0.02). There was a reduced or even inverse CD4:CD8 ratio, which generally persisted 3-4 weeks. Lymphocyte transformation assays demonstrated significantly reduced reactivity in 5 of the 9 patients who completed the 7-day course, whereas 4 individuals exhibited an unexpected elevation in the T cell response to mitogens and common antigens. Parallel laboratory studies showed a significant decrease in the erythrocyte sedimentation rate (P less than 0.05), rheumatoid factor titer (P less than 0.04), and total immunoglobulin values (P less than 0.01), as well as a reduction in C-reactive protein levels, in 7 of the 9 patients. Clinically, there was a significant reduction in the Ritchie articular index (P less than 0.05) and in the number of swollen joints (P less than 0.04). Adverse effects were urticaria in 2 patients, which led to withdrawal of therapy in 1 of them, and chills with fever, suggestive of a lymphokine release syndrome, in another 2 patients. Only low levels of human anti-mouse immunoglobulin antibodies developed (not exceeding 1.7 mg/liter). It was therefore possible to repeat the treatment cycle, achieving still better efficacy, in 4 of the patients (reductions in the Ritchie index and the number of swollen joints P less than 0.02). Our findings indicate that treatment with monoclonal antibodies against the CD4 antigen leads to immunomodulation which results in clinical benefits, at least during initial observation periods (up to 6 months postinfusion). However, it remains to be determined whether long-term

remission can be induced with this therapeutic approach. The use of immunosuppressive therapies or repeated antibody treatments will have to be considered.

PMID: 1994909 [PubMed - indexed for MEDLINE]

1: J Immunol 1990 Jun 15;144(12):4587-92

Related Articles, Books, LinkOut

Mechanisms of anti-CD4-mediated depletion and immunotherapy. A study using a set of chimeric anti-CD4 antibodies.

Alters SE, Sakai K, Steinman L, Oi VT.

Program in Cancer Biology, Stanford University School of Medicine, CA 94305.

A family of rat-mouse chimeric anti-murine CD4 antibodies was used to study the mechanisms of anti-CD4-mediated depletion and immunotherapy. The chimeric antibodies retain identical affinity and specificity as the therapeutically effective prototype antibody, rat GK1.5, but are of different mouse isotypes. GK1.5 gamma 1, GK1.5 gamma 2a, and GK1.5 gamma 2b are significantly more effective at CD4+ cell depletion than rat GK1.5 when low doses of antibody are administered. In contrast, no depletion is seen with GK1.5 gamma 3 at any dose. Depletion of CD4+ cells in vivo is not correlated with either the ability of the antibody to mediate C-dependent cytotoxicity or antibody-dependent cell-mediated cytotoxicity in vitro, implying that additional antibody-mediated cytotoxic mechanisms occur in vivo. The chimeric antibodies were used to investigate the mechanism of GK1.5-mediated immunotherapy in a prototypic model of T cell-mediated autoimmunity, experimental allergic encephalomyelitis. Mice treated with a single dose of 100 micrograms of either GK1.5, GK1.5 gamma 1, or GK1.5 gamma 2a showed significant recovery within 72 h. In contrast, mice treated with 100 micrograms of GK1.5 gamma 3 showed only marginal improvement within the first 72 h and regressed within 5 days of treatment initiation. These data suggest that anti-CD4-mediated immunotherapy of murine experimental allergic encephalomyelitis is correlated with depletion of CD4+ cells.

PMID: 1972161 [PubMed - indexed for MEDLINE]

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☐ 1: Transplantation 1991 May;51(5):1072-5

The effect of partial in vivo depletion of CD4 T cells by monoclonal antibody. Evidence that incomplete depletion increases IgG production and augments in vitro thymic-dependent antibody responses.

Cowdery JS, Tolaymat N, Weber SP.

Department of Internal Medicine, University of Iowa College of Medicine, Iowa City 52242.

In vivo depletion or inactivation of CD4 T cells by monoclonal antibody inhibits of T-cell-dependent immune responses and, in some cases, ameliorates clinical autoimmune disease. Impairment of T cell function occurs in situations where mice are treated with relatively large doses of anti-CD4 antibody. When adult (C57BL/6xDBA/2)F1 mice were treated with a low dose of anti-CD4 antibody augmentation of certain thymic-dependent responses occurred. Twice-weekly injections of 50 micrograms of monoclonal antibody GK1.5 for a period of three weeks resulted in a 50% reduction of splenic CD4 T cells. Mice that were partially depleted of CD4 T cells exhibited a 55% increase in serum IgG levels with a 165% increase in serum IgG1. Simulation of spleen cells from these mice with LPS in a significant increase in differentiation of IgG secretion. When spleen cells from partially CD4-depleted mice were challenged in vitro with SRBC, they mounted a direct PFC response that was more than four times the observed PFC response of mice that received either saline or rat IgG. These findings indicate that partial depletion/inactivation of CD4 T cells by in vivo administration of anti-CD4 monoclonal antibody results in a significant augmentation of certain T-cell-dependent humoral responses.

PMID: 1674386 [PubMed - indexed for MEDLINE]

☐ 1: Clin Exp Immunol 1993 Sep;93(3):301-7 Related Articles, Books, LinkOut

In vivo treatment with a monoclonal chimeric anti-CD4 antibody results in prolonged depletion of circulating CD4+ cells in chimpanzees.

Jonker M, Slingerland W, Treacy G, van Eerd P, Pak KY, Wilson E, Tam S, Bakker K, Lobuglio AF, Rieber P, et al.

Centocor Malvern, PA.

Chimeric M-T412 (cM-T412), an anti-CD4 antibody, was tolerated in chimpanzees at a dosage of 5 mg/kg per day for up to 7 consecutive days, or 5 mg/kg per dose, twice weekly for 4 weeks. All cM-T412-treated chimpanzees showed a prolonged CD4-cell depression. Weak chimpanzee antibody responses to chimeric M-T412 were observed. One of the chimpanzees on the biweekly dosage regimen exhibited a hypersensitivity reaction immediately after receiving its seventh dose. Following supportive treatment, the animal recovered and remained asymptomatic during the non-treatment observation period. The hypersensitivity reaction was not an unexpected response considering the animal received repeated intermittent i.v. administration of a foreign protein. This animal also showed a chimpanzee antibody response to chimeric M-T412 after the seventh dose. Chimeric M-T412 also induced an anti-cM-T412 response in some of the other animals. The level of this response was lower than the anti-mouse responses observed in animals treated with murine anti-CD4. Moreover, the anti-cM-T412 response was mainly directed to idiotypic determinants. The decrease in CD4+ cells observed for all chimeric M-T412-treated chimpanzees is an expected effect of the anti-CD4 antibody. The duration of this CD4+ cell decrease is, however, much longer than observed for other CD4-specific MoAbs described. No selective loss of either memory or naive CD4+ cells was observed after either the single, 7-day or twice-weekly treatments. The CD4+ cell depression was reversible, although individual variation in time to recovery was observed. Therefore, cM-T412 could be a good candidate for clinical use in autoimmune conditions.

PMID: 8103714 [PubMed - indexed for MEDLINE]

☐ 1: Biotechnology (N Y) 1992 Nov;10(11):1455-60 Related Articles, Books, LinkOut

"Primatization" of recombinant antibodies for immunotherapy of human diseases: a macaque/human chimeric antibody against human CD4.

Newman R, Alberts J, Anderson D, Carner K, Heard C, Norton F, Raab R, Reff M, Shuey S, Hanna N.

IDEC Pharmaceuticals Corporation, La Jolla, CA 92037.

Immunoglobulin variable region genes from non-human primates, cynomolgus macaques, were shown to have 85%-98% homology with human immunoglobulin sequences and yet macaques are phylogenetically distant enough to respond against conserved human antigens. Immunoglobulin genes were isolated from monkeys immunized with human CD4 antigen and a human/monkey chimeric anti-CD4 antibody with 91-92% homology to human immunoglobulin framework regions was cloned and expressed. The antibody has an apparent affinity of 3.2 x 10(-11) M and exhibits potent immunosuppressive properties in vitro.

PMID: 1369023 [PubMed - indexed for MEDLINE]

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☐ 1: Clin Exp Rheumatol 1990 Jul-Aug;8 Suppl 5:81-8

Immunological treatment of rheumatoid arthritis.

Sany J.

Service d'Immuno-Rhumatologie, Hopital Saint-Eloi, Montpellier, France.

Till now the therapeutic immunomodulation of rheumatoid arthritis (RA) has been non-specific, using either slow acting drugs which act mainly but not exclusively on macrophages (gold salts) or on T CD4+ cells (D penicillamine), or immunostimulating agents (Levamisole) or immunodepressive drugs which do not affect a specific subpopulation of lymphocytes. Various other therapeutic approaches such as dietic manipulations, steroid pulses and plasmapheresis have been proposed. Methotrexate is a very interesting development in the treatment of RA. However, the results of such treatments on the long term outcome of the disease have been unsatisfactory. Early and associated treatments must be studied. After the interesting experimental results obtained with thoracic duct drainage, a partially specific immunotherapy acting mainly on CD4+ T cells has been developed using cyclosporin A and total lymphoid irradiation. However, a more specific immunotherapy of RA may be considered, using monoclonal or polyclonal anti-HLA class II antibodies or anti-CD4 monoclonal antibodies. Immunomodulating treatments with cytokines or anticytokines, anti-T receptor monoclonal antibodies, anti-idiotypic antibodies, and vaccination with T cell clones or synthetic peptides are possibilities of major interest for the future.

Publication Types:
- Review
- Review, Tutorial

PMID: 2245532 [PubMed - indexed for MEDLINE]

1: Lancet 1991 Jun 15;337(8755):1477

Comment in:
- Lancet. 1991 Aug 3;338(8762):321.

Are CD4 antibodies and peptide T new treatments for psoriasis?

Poizot-Martin I, Dhiver C, Mawas C, Olive D, Gastaut JA.

Publication Types:
- Letter

PMID: 1675339 [PubMed - indexed for MEDLINE]